## REMARKS

Reconsideration of the rejection of all claims is respectfully requested in view of the following remarks.

### *Status of Claims*

As a convenience to the Examiner, the status of all claims, and the text of all pending claims, are presented above using the format of the current practice. No claims are further amended herein, and the claims remain as presented or amended in the Response to Restriction Requirement and Second Preliminary Amendment filed September 5, 2002.

### *Information Disclosure Statement*

The Examiner's attention is called to the further Information Disclosure Statement filed herewith in which are cited four patents to Ikeda. These four Ikeda references are part of a series of 20 or so patents that all derive from a U.S. application filed on June 19, 1996 based on a Japanese priority application filed June 20, 1995. This Ikeda series of patents claims numerous combinations of an insulin sensitivity enhancer with at least one other drug, including a α-glucosidase inhibitor, aldose reductase inhibitor, biguanide, statin compound, squalene synthesis inhibitor, fibrate compound, LDL catabolism enhancer and angiotensin converting enzyme (ACE) inhibitor, and "other antidiabetics," and a variety of uses thereof. The disclosure of each of these patents is understood to be identical, and therefore the four patents cited are believed to be appropriately representative of the disclosure. These

particular patents were chosen in that they claim methods using a combination of an insulin sensitivity enhancer with a statin compound for various uses:

- A method for reducing the amount of active components administered to a diabetic patient (USP 6,103,742);
- A method for treating diabetic complications in a mammal (USP 6,121,295);
- A method for reducing the side effects of active components administered to a diabetic patient (USP 6,169,100); and
- A method for treating circulatory disorders in a mammal in need thereof (USP 6,384,062).

These Ikeda will be discussed further below.

The further Information Disclosure Statement also includes a number of literature references which are believed to be relevant to the state of the art at around the time of the present invention.

***Claim Rejections – 35 U.S.C. § 103***

All claims have been rejected under 35 U.S.C. § 103(c) as being unpatentable over Hirsch *et al.* in view of Hirai *et al.* further in view of Budvari *et al.* This ground for rejection is respectfully traversed.

Present independent claim 22 is directed toward the elected invention, being a method for treating **diabetic neuropathy** by administering an effective amount of the statin drug (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof (hereinafter the "Agent"). The dependent claims are directed toward the method of claim 22

also including administration of at least one other drug used for treating diabetes or complications of diabetes, and/or the salt form or dosage of the Agent.

At the time of the present invention, the use of statin drugs as a HMG-CoA reductase inhibitor in the treatment of hyperchloesterolemia was well established, including the treatment of diabetics having hypercholesterolemia and/or large vessel impairments such as atherosclerosis. There also was speculation or unsubstantiated generalizations in some patent and/or literature references, that the administration of statin may also have a beneficial effect on a wide range of the various complication of diabetes, including microvascular complications. However, prior to the work of the present inventors as disclosed in this application, there was no demonstration that statins actually could benefit the microvasculature, and treat disease conditions such as diabetic neuropathy and impaired nerve blood flow in patients suffering from diabetes. It is therefore respectfully submitted, as detailed further below, that the prior art speculation might, *at best*, make the presently claimed methods "obvious to try." However, as the Examiner is certainly aware, "obvious to try" cannot support *prima facie* obviousness.

Referring to the specific grounds for rejection, the Examiner cites Hirsch as teaching "HMG-CoA reductase inhibitors for the normalization of vascular endothelial dysfunction," characterizing the disclosure at page 2, lines 1-14, as stating that "the HMG-CoA reductase inhibitors may reduce the effects of vascular endothelial dysfunction that may contribute to microvascular complications." The secondary reference, Hirai. is cited as teaching "the applicants' preferred statin drug as an old and well-known drug possessing the same activity as the HMG-CoA reductase inhibitors of the primary reference." The tertiary reference,

Budavari, is cited as teaching that pioglitazone is a well-known insulin sensitizing agent used to treat diabetics.

This ground for rejection is respectfully traversed. Applicants acknowledge that Hirai teach the Agent as a HMG-CoA reductase inhibitor, and that Budavari teach pioglitazone as an insulin sensitizing agent used to treat diabetes. However, it is respectfully submitted that neither Hirsch alone nor in combination with the other references adequately suggests or teaches persons skilled and knowledgeable in this art at the time of the present invention, to use the Agent, or any other HMG-CoA reductase inhibitor, for the treatment of diabetic neuropathy, with a reasonable expectation of success.

Hirsch et al, WO 94/13063 (no U.S. equivalent found) is directed toward the use of HMG-CoA reductase inhibitors in the normalization of vascular endothelial dysfunction. The reference notes at page 1 that in normal basal physiological state the endothelium provides a nonthrombotic, noninflammatory vascular lining, and that the vascular endothelium plays a critical role in mediating primarily vasodilation, but also vasoconstriction. Continuing at page 2, the reference notes that the normal state of the cardiovascular system is one of active vasodilation dependent on the continuous generation of NO by the vascular endothelium, and that in the absence of the endogenous vasodilator, the blood vessels constrict, resulting in a decrease in the blood supply. The reference then speculates (in the passage referred to by the Examiner) on a wide variety of conditions to which *these effects may contribute*:

> These effects may contribute to the production of ischemic syndromes such as angina pectoris, myocardial infarctions, coronary artery disease (CAD), hypertension, cerebrovascular accidents, transient ischemic attacks, chronic obstructive pulmonary disease, chronic hypoxic lung disease, pulmonary hypertension, renal hypertension, chronic renal disease, microvascular complications of diabetes and vasoocclusive complications of sickel cell anemia.

Despite this broad speculation of other conditions to which "these effects may contribute" (including microvascular complications of diabetes"), the reference focuses *only* on the treatment comprising "the administration to a patient at risk of developing atherosclerosis or a patient in whom the disease has been diagnosed with an HMG-CoA reductase inhibitor to restore endogenous vascular endothelium dependent activities including improving the normal dilation capacity of the endothelium." (Hirsch, page 5 under the heading "Detailed Description of the Invention"). The reference then again speculates at page 6, lines 5, listing essentially the same variety of "ischemic syndromes" as quoted above that *may* be treated by the method of their invention.

It is particularly noteworthy, however, that Hirsch neither presents nor cites any support for extrapolating the noted effect of HMG-CoA reductase inhibitors on endothelial dysfunction in the *large blood vessels,* to the *microvasculature* involved in the diabetic neuropathy and impaired blood flow of the present application. See, for example, the discussion of references at page 2, beginning at line 15, dealing with, *e.g.*, atherosclerosis, coronary artery disease vascular endothelial dysfunction in the human forearm, *etc.* See, also, Hirsch Example 1, which reports on a selection of patients undergoing angioplasty, in which there is no mention that any of such patients was diabetic, or no disclosure relating to any effect on the microvasculature. In fact, Hirsch would seem to discourage such a speculative extrapolation when it notes at page 2, lines 26 to 30, that the effects on different "vascular beds" varies, and that the vascular beds are physically separate entities.

Contemporaneous and post-invention reviews confirm that persons skilled in the art at the time of the invention did not consider that HMG-CoA reductase inhibitors to be a treatment option for diabetic neuropathy.

For example, several years after the May 1995 publication of the cited Hirsch PCT application, a series of articled relating to diabetic neuropathy were published, which are believed to arise out of a symposium presented at the American Diabetes Association Meeting in Chicago in 1999. The introduction by Apfel[1] notes the "special focus" of the symposium was on novel therapeutic approaches that have been developed for diabetic neuropathy as a result of new and greater understanding of the disorder. However, nowhere in the introductory article, nor in the Vinik[2] and the Parry[3] reviews that follow, is there any mention of using a statin in the treatment of diabetic neuropathy. Thus, Vinik separately discusses therapeutic interventions for each of distal symmetric polyneuropathy, autonomic neuropathy and controlling the pain of diabetic neuropathy, but the use of HMG-CoA reductase inhibitors or statins are nowhere mentioned. Similarly, the abstract of Parry begins with the observation that, "(t)he only strategy shown to be consistently beneficial in the treatment of diabetic neuropathy is meticulous control of blood glucose," and there is no mention of the use of a statin or HMG-CoA reductase inhibitor as an alternative strategy.

Other articles or letters cited in (and submitted with) the further Information Disclosure Statement discuss one or more of endothelial dysfunction, diabetic conditions, and the use of satins or other treatment strategies, but their focus is on endothelial dysfunction or atherosclerosis relating to large vessels (brachial, coronary, forearm resistance *etc.*), but there is no suggestion or teaching of the use of a statin or HMG-CoA reductase inhibitor in the treatment of the microvasculature, no less in the treatment of diabetic neuropathy.

Finally, the Ikeda disclosure is directed most particularly to their specific insulin sensitivity enhancers, but the insulin sensitivity enhancers are claimed in combination with

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[1] Apfel, "Introduction to Diabetic Neuropathy", Excerpta Medica, Inc., 1999, p. 1S.
[2] Vinik, "Diabetic Neuropathy: Pathogenesis and Therapy", Excerpta Medica, Inc., 1999, pp. 17S-26S.
[3] Parry, "Management of Diabetic Neuropathy", Excerpta Medica, Inc., 1999, pp. 27S-33S.

many other antidiabetics, among which are included statin compounds. However, only two examples are included in the patents, and these examples have no bearing whatsoever on any combination of the insulin sensitivity enhancers with a statin compound. Example 1 tests the effect of pioglitazone hydrochloride in combination with α-glucosidase inhibitor, showing that the levels of blood glucose and hemoglobin A levels were lowered more with the combination that with either drug alone. Example 2 tests the effect of pioglitazone hydrochloride in combination with an insulin secretion enhancer, and concludes that the increase in blood sugar following glucose loading was remarkably inhibited by the combined administration of the combined drug as compared with the administration of either drug alone.

Each Ikeda patent concludes with a speculative generalization that the claimed pharmaceutical composition is useful for the prophylaxis and treatment of a broad list of diabetic complications, including diabetic neuropathy. However, such a non-supported, speculative listing regarding a combination product which may or may not include a statin, adds nothing to the knowledge of the art with respect to statins, which art in any event did not consider statins as a viable treatment for diabetic neuropathy, as shown above. Therefore, it is respectfully submitted that the Ikeda disclosure does not even rise to the level of "obvious to try."

In contrast to the speculative and unsupported comments of Hirsch or Ikeda, the present application disclosure is *particularly* directed toward the treatment of diabetic neuropathy, specifically in improving nerve conduction velocity and nerve blood flow in diabetic patients by administration of a statin. Moreover, the Agent (rosuvastatin) and atorvastatin are tested in Example 6 in an accepted animal model against one another and against a non-diabetic control and a non-treated diabetic control, with respect to sciatic nerve motor conduction velocity, saphenous nerve sensory conduction velocity and sciatic nerve blood flow. In each instance, the treatment with the statin was effective in substantially raising the nerve conduction velocity and nerve blood flow values above that of the untreated diabetic control. Applicants have thus provided disclosure specifically directed toward the treatment of diabetic neuropathy by use of certain statins, and have also provided exemplary

evidence in support thereof, contrary to the mere off-hand and speculative comments of Hirsch and Ikeda.

Under these circumstances there may be, *at best*, an argument that it would have been "obvious to try" the use of a statin for the treatment of diabetic neuropathy. However, Federal Circuit case law establishes that "obvious to try" does not give rise to *prima facie* obviousness. For example, this was made clear by the Federal Circuit in *Merck & Co. Inc. v. Danbury Pharmacal Inc.*, 8 USPQ2d 1793, 1816 (Fed. Cir. 1988):

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art. Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure.
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> In Re Dow Chemical Co ., 837 F.2d 469, 473 [ 5 USPQ2d 1529, 1531] (Fed. Cir. 1988) (citations omitted).
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> Thus, **the governing standard is emphatically not whether a particular method or process leading to an invention would be "obvious to try,"** In Re Fine, 837 F.2d 1071, 1075 [ 5 USPQ2d 1596, 1599] (Fed. Cir. 1988), **but whether such an experiment would have been expected to succeed**. In Re Merck, 800 F.2d 1091, 1097 [ 231 USPQ 375, 379-80] (Fed. Cir. 1986). Moreover, this expectation must be measured with deliberate avoidance of hindsight assessment. Id . However, the standard does not require "absolute predictability." Id . "Only a reasonable expectation that the beneficial result will be achieved is necessary to show obviousness." Id .

(Emphasis added). The Federal Circuit again addressed the insufficiency of "obvious to try" in *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* 18 USPQ2d 1016, 1022 (Fed. Cir. 1991):

> The district court specifically found that, as of 1983, none of the prior art references "suggest[s] that the probing strategy of using two fully-redundant [sic] sets of probes, of relatively high degeneracy [sic], to screen a human genomic library would be likely to succeed in pulling out the gene of interest." 13 USPQ2d

> at 1768. **While it found that defendants had shown that these procedures were "obvious to try," the references did not show that there was a reasonable expectation of success.** See In re O'Farrell, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1680-81 (Fed. Cir. 1988).
>
> Defendants challenge the district court's determination, arguing that, as of September 1983, one of ordinary skill in the art would have had a reasonable expectation of success in screening a gDNA library by Lin's method in order to obtain EPO. We agree with the district court's conclusion, which was supported by convincing testimony.

(Emphasis added). See also the District Court decision in *Spalding & Evenflo Companies Inc. v. Acushnet Co.,* 13 USPQ2d 1081, 1097 (D. Mass. 1989), where the court noted, in holding the claims not to be obvious:

> Thus **the critical inquiry is not whether it would have been obvious to try** a particular method or process leading to an invention (blending ionic copolymers to make a golf ball cover), **but rather whether such an experiment would have been expected to succeed** (specifically, achieve an increase in coefficient of restitution from blending ionic copolymers to form a golf ball cover). See In re Merck, 800 F.2d 1091, 1097 [ 231 USPQ 375, 379-380] (Fed. Cir. 1986).

Therefore, neither Hirsch alone, nor in combination with the other applied references, supports a case of *prima facie* obviousness.

***Conclusion***

In view of the above remarks and the additional documents cited and provided with the further Information Disclosure Statement submitted herewith, it is submitted that the applied combination of references does not support the obviousness rejection of the present

claims. Accordingly, the withdrawal of this rejection and the allowance of all claims are believed to be in order, and are respectfully requested.

**EXCEPT** for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
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